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THE SCIENTIFIC INVESTIGATION OF CANCER

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WE may treat the subject of cancer from two points of view, namely, from that of the scientific investigator who studies it as a natural phenomenon and ascertains the laws of its origin and development, and from that of applied science, medicine, which is mainly concerned with the eradication of the disease. In the natural course of events, scientific analysis must precede the utilitarian attempts at control. I shall treat the subject of cancer purely from the viewpoint of scientific analysis. This analysis is not yet completed and on this occasion I shall endeavor to tell something of what science has discovered about cancer, following a study which really does not date much further back than twenty years.

Scientific investigation starts with the most obvious and gradually penetrates into the more remote. Experiences are the starting point for investigation; experiences that call forth pain or pleasure, especially those that call forth pain, which do not fit into the rest of our life, which disturb its real or imagined harmony. In its origin, therefore, science is utilitarian. It is a direct struggle with the enemies of our peace of mind and of our body. Only gradually, through the greater maturity of our experiences, does reality become the object of our interests in this struggle with the emotions, and from now on we are no longer guided directly by them in our investigations, but the latter become transformed into a dispassionate search for the relations of facts. We seek to complete the picture of reality which at first was only a by-product of other efforts. This now becomes our real problem. The investigations have passed beyond the primitive, utilitarian stage. Eventually, however, this study of reality for its own sake leads to results which again serve our utilitarian purposes better than a direct attack of the problems from a so-called "practical" point of view. Wireless telegraphy, diphtheria antitoxin, the eradication of yellow fever were possible only on the basis of purely scientific analysis, such as is carried on in the case of cancer research at the present day. The greatest technical progress has been accomplished and may be expected to bring the best results in the future by attacking the problem on the basis of a dispassionate philosophical analysis of reality. This analysis transforms thunder and lightning, which at first called forth only feelings of awe and fear, into phenomena of electricity, acoustics and optics, and teaches us their oneness with the phenomena which help to maintain life. The growth of bacteria, which cause disease and death, on the one hand, is seen to play a wider rôle in the economy of life, to be indispensable for the maintenance of life in the higher animals.

It is not otherwise with the subject on which I have been asked to write. What at first we consider a disease, a scourge which fills us with fear and despair, will be seen to be but a particular phenomenon of growth comparable in a certain respect to the development of the egg into the adult, to the restitution of an extremity in one of the more primitive amphibia and to the healing of the wound in a human body after a cut or a bruise.

In cancer we deal with an essentially similar phenomenon—with the multiplication of the small units of our body, the cells. In a definite, usually sharply circumscribed and relatively small area such cells begin to proliferate; they multiply to an unusual degree; they make their way into the deeper parts of the body, destroy the neighboring tissues, penetrate often into lymphatics or blood vessels, are carried to distant parts of the body—lung, liver or elsewhere—settle here and give origin to secondary growths, the so-called metastases. Not all new formations of this kind, which are generally called tumors, are equally destructive. Some merely grow slowly and form a prominence without penetrating into neighboring tissues. These are the so-called benign tumors. The destructive tumors are called cancers. Almost any tissue in the body, almost any cells may, under certain conditions, begin to grow in this malignant, cancerous manner and, according to the kinds of cells that have thus proliferated, different types of cancer have been distinguished, as, for instance, *carcinoma*—the cancer of the cells covering the surface of the body and the body cavities, the epithelial cells; and *sarcoma*—the cancer of the tissues connecting the various surface and glandular structures of the body. But these are, for our purposes, differences of minor importance. The essential fact is this: in cancer we are dealing with a cell multiplication similar to that which leads to the building up of the normal organism, the difference between normal growth and cancerous growth being as follows:

During the development from the egg to the adult organism, the multiplying cells and the developing tissues show a definite relation to one another, which is essentially hereditarily fixed. In cancer, however, certain cells or tissues fall out of this normal scheme of predetermined growth; they are no longer kept in bounds through the agencies which restrain the development of other parts of the body, and this leads to the formation of monstrosities. We may then conclude that the same laws which ultimately determine all cell and tissue growth also underlie cancerous growth. These laws are fundamentally those regulating the physical and chemical changes which take place in the protoplasm. But added to these *general* causes of growth, which cancer has in common with embryonic development and the process of repair after the loss of parts of the body—the so-called regenerative growth—there must be a special factor which is responsible for the excessive growth-energy and destructive capacity of certain tissues or cells in the body which distinguishes them as cancerous growths from other kinds of growths. To find this special factor or rather this special set of factors constitutes the fundamental cancer problem.

In my introductory remarks I stated that certain experiences in life of a more or less emotional character are the starting point for investigation, and that only gradually do these investigations become dispassionate, objective, do they come into contact with neighboring fields of research and broaden into an attempt to understand reality. Hand in hand with this enlargement of the concept of the problem we find a simultaneous widening of the range of objects now considered as more or less related to the original object of investigation, and a greater refinement in the methods of research. At first only human cancer was considered. It is only recently that we turned with interest to other organisms and discovered that cancer exists in all classes of vertebrates—although with unequal frequency—and that somewhat related phenomena are even to be observed in plants. At first we were satisfied with the observation of human tissues with the naked eye and with statistics concerning the frequency and distribution of human cancer; later there were added microscopic investigations with gradually accumulating refinements. These in turn were reinforced with experimental methods in which were recorded observations of the growth of cancers in animals which had been inoculated with tumor. And then we began to study experimentally the conditions under which cancer developed spontaneously and under which the development of spontaneous cancer can be prevented in animals, and the reactions of normal tissues under various abnormal conditions.

The experimental study of cancer is as necessary as the experimental study of all other problems. Mere observation confronts us usually with a considerable number of variable factors, and when we observe a sequence to a certain group of factors, observation alone does not usually permit us to decide which factors are really causative and which merely accidental. Through experiment we can at will isolate or combine various factors and thus alone find the real causes. Experimentation in the case of cancer does not only consist in the artificial inoculation of cancer—which, by the way, is technically not very different from the injections of substances under the skin in human beings, and therefore not very painful—but also in the systematic breeding of certain animals and in varying the conditions of life in which animals are kept. In this way problems can be solved whose solution can hardly be attained if we restrict ourselves to observations of human cancer, because of the complicated conditions found in human society.

We have now determined what is meant by tumor and cancer, the general distribution of cancer and the methods of investigating the cancer problem. Let us then follow the threads of investigation a little farther and consider some of the results obtained by experimental means. Here we will take up in turn the three problems, namely, the conditions that lead to cancer, the reaction which takes place in the body against cancer growth, and lastly some properties of cancer cells—and secondarily of normal cells—which have been discovered as a result of cancer investigations.

In analyzing the origin of certain phenomena, we are apt to take one definite circumstance as the cause of a succeeding event. This is the procedure which we usually follow in our daily life. But a more careful analysis of any phenomenon will usually reveal to us the very much more complicated relation it bears to other phenomena. The more we search, the more apt we are to find that there are a number or rather a multitude of factors which at the very beginning work together, shaping the event which interests us. Among these factors we can discern some which seems to us of greater importance, more specifically related to the event under discussion and others which apply not alone to this specific event or to a relatively restricted number of events, but equally well to a large number of other experiences, not necessarily related to the one under consideration. For instance, to mention a factor belonging to the second category, the temperature which is required to sustain life processes in general and therefore also in particular cancer growth. The relation between temperature and cancer growth is therefore not a specific one, but one which cancer growth shares with other life processes. While a certain temperature, then, is one of the conditions necessary for the development of cancer, it is not a specific condition and therefore not a cause in the strictest sense of the word.

We know that not one single factor is the cause of cancer, but we have discovered a number of conditions all more or less specifically related to cancer growth. Provisionally these may be divided into two classes, namely, internal and external factors. By internal factors we mean such as are operative within the organism, apparently conditioned mainly by the organization of the animal and at a place not accessible to a direct experimental change. The external factors consist of conditions operative in the environment of the cells which give origin to cancer, either within or without the whole organism of which the cancer cells form a part. The external factors are more accessible to experimental control than the internal. The external factors which set up changes in the cells and tissues are usually only the first link in the chain of circumstances which ultimately ends in the production of cancer. And this link we may generally call a *stimulus.*

Let us then first consider some of the internal factors and later the external factors which lead to cancer growth. One of the most important internal factors which has been thoroughly established within recent years, at least in the case of animal cancer, is heredity. Our attention was first drawn to the possibility that heredity might play a part in the origin of cancer, through observations which we as well as other investigators, made some eighteen years ago. It was found that a surprising multiplicity of cancers occurred in certain cages in which animals were kept, especially rats and mice, and that the varieties of cancer which appeared under those conditions were in each case identical. This led to the conclusion that cancer was so often found in those cages because the animals living there belonged to the same family.

There are other possible explanations for the frequent occurrence of cancer in animals kept in the same cage or breeding place. It might have been that the cancer spread through infection from one animal to another. Indeed, in the case of man, the alleged greater frequency of cancer in certain regions has been explained by some observers on the basis of the infectiousness of cancer. However, I may state here that no undisputed case, in animals or in man, has ever been recorded where cancer was known to have spread through infection caused by a microorganism. This lack of infectiousness, however, does not entirely exclude the possibility of the presence of microorganisms in certain cancers—a possibility to which I shall have occasion to refer later. There are certain cases in which metazoic parasites are undoubtedly responsible for the so-called "endemic" occurrence. We have, however, been able to decide the question as to the usual cause of the occurrence of identical cancerous growths in animals by showing that hereditary conditions play a paramount rôle. For this purpose we used mice, which are perhaps most suited to such experiments, since they are not long-lived animals. We kept them in families separated from each other throughout a number of years, but otherwise absolutely under the same conditions as far as climate and food were concerned. Now we found that each family had a definite cancer rate which remained approximately *constant throughout succeeding generations.* While in some strains cancer occurred in about 70 per cent. of all females, in others it occurred in only 2 to 3 per cent. If we crossed two mice belonging to strains with different cancer rates, we found that in a considerable number of cases the offspring followed approximately the cancer rate of the parent with the higher cancer percentage; in other cases, however, the offspring followed the parent with the lower cancer percentage. *There is therefore not the least doubt that cancer in animals is hereditary.* And not only is the cancer frequency hereditary, but *also the* age at which cancer most frequently appears in each family. The hereditary transmission of the cancer age is independent of the frequency. Thus it may occur that if we compare two families we may find that cancer is about equally frequent in both, but that it appears in one most frequently in middle life, while in the other it usually develops in later life. And these conditions are constant in succeeding generations.

Does this conclusion apply equally to cancer in man? The complicated conditions in human society make it very difficult to interpret statistical data with the same definiteness as in the case of animals. There are, however, indications which make it very probable that *in man also heredity is a definite factor.* We know that some races are almost immune to cancer, as, for instance, the American Indian, the Negro in Africa, and some aborigines of Australia and the South Sea Islands. It is very probable that this immunity to cancer is not due to the differences in food or to climatic conditions. Europeans removing to these regions are not immune. Furthermore, we note that the negro in America has a much higher cancer rate than the negro in Africa. This may possibly be referable to the interbreeding which has taken place among the negroes and whites in this country. Definite data for man which could answer this question are, however, lacking, and until more exact investigations in this direction can be undertaken we must abstain from making final decisions as to this point. The observation that among white people the cancer rate differs relatively little in various civilized countries does not speak against the existence of a heredity factor. It might merely indicate that the hereditary disposition to cancer is about equal in different families or strains. Furthermore, in human society intermarriages have been so constant and so frequent that differences between various families which might have existed to a greater degree at earlier stages of development may gradually have been eliminated or obscured. It is, however, well known that in certain human families cancer has been very frequent. Only recently a very interesting observation was published concerning two sisters, who died within a very short time of one another, and were both found to have been affected by the same *very rare kind* of cancer. While it is perhaps possible to explain all such occurrences among human beings as referable to the laws of chance, the facts established in the case of animals rather suggest that in human cases too heredity may be an important cause.

There are other conditions which may under certain circumstances act as internal factors. In the human being certain very peculiar tumors are found which by their general appearance recall the structure of embryonic tissues. By embryonic tissue we mean those structures which are intermediate between the ovum and the adult organism. These tumors are therefore called embryomata and they are found especially within the generative glands. It has been recently observed that eggs within the generative glands may begin spontaneously to undergo a certain development—to develop without fertilization. According to our observations such a development may proceed even to the early formation of the central nervous system. Such structures are, however, usually destroyed after a period of temporary growth; but it seems that under certain conditions they can develop into malignant tumors, malignant embryomata, or teratomata. The factors therefore which favor the fargoing parthenogenetic development of the ova must be considered as in some cases playing the part of internal factors leading to the production of cancer.

Developmental malformation is a third factor which may cause cancer. These tumors are frequently found at an early age, but they may become apparent only in later life. In either case they originate during the period of embryonic development. We know that developmental errors are not infrequently found in man as well as in animals. Not rarely cells are misplaced, partly or entirely separated from the normal environment. In most cases such abnormally placed cells do not result in serious consequences, but, in some, as we have said, they become the starting point for malignant tumors. Pigmented moles may be considered as developmental errors and it is a well-known fact that under certain conditions favorable to cancerous growth they have become malignant tumors. Thus again *indirectly* may heredity play a part in the origin of cancer.

EXTERNAL FACTORS

Let us now briefly consider the external factors to which we referred. Generally speaking any mechanical stimulus acting over a long period of time and leading to inflammatory conditions may produce cancer. Thus we know that long-continued burning of the skin by carrying stoves, as the natives of Kashmir do, and long-continued action of Roentgen rays, extending over a number of years without the available precautionary means, have led, in many cases, to the production of cancer. Chemical stimuli also may lead to cancer. It is well known that in certain trades cancer is more frequent because of the action of the chemicals used. Paraffin workers are not rarely affected by cancer of the skin; aniline workers develop cancer of the bladder. But more interesting than these general chemical actions is the fact that certain chemical substances given off by organs within the body which normally have a stimulating action on the growth of certain tissues may on the strength of this stimulating action be factors favorable to the development of cancer. Thus it has been recently demonstrated that extirpation of the ovaries in animals at a certain period of their life may greatly reduce the occurrence of cancer of the breast in those animals. This is, in all probability, due to the fact that a certain substance given off by the ovary which normally stimulates the growth of the mammary gland is removed through the extirpation of the ovaries. Apparently any external condition which causes long-continued growth processes in cells may in consequence of this stimulating action be a factor in the origin of cancer, and if we learn to eliminate such action we may to some extent prevent the development of cancer in a certain percentage of cases.

We have now learned of a number of causes for this abnormal cell proliferation which we call cancer. We know furthermore that internal and external factors must cooperate in the development of cancerous tissue. But it is very probable that the ratio between the number of internal and external factors necessary to obtain definite results is not fixed. The larger the number of external factors the smaller, in all probability, need the requisite number of internal factors be. For instance, it is probable that very long-continued action of Roentgen rays may lead to the production of cancer in persons in whom the heredity factor may be very weak.

Stimuli, such as those which lead to the production of cancer, chemical as well as mechanical, also cause growth processes in normal tissue. We know that in lower animals parts of the body which have been lost, may be replaced; that in higher animals wounds will heal; that certain chemical substances call forth growth processes which are not cancer. For instance, the placenta, through which the fetus is attached to the mother, grows in response to a combined action of chemical and mechanical stimuli; ova can develop parthenogenetically (without fertilization) under the influence of various stimuli. But in all those cases the stimulus leads to only a temporary proliferative activity of the cells and tissues. Sooner or later, the tissues return to their former equilibrium in which proliferation is very limited or entirely absent. It is not so in cancer. Cells which through various agencies have once become cancerous may be destroyed; but where they are not exterminated, provided sufficient nourishment is obtainable and other conditions necessary to their growth permit it, they proliferate eternally. Cancer cells, then, differ from normal cells in so far as the stimulus which in normal cells produces only a temporary growth, in the cancerous transformation produces an endless increase in cell proliferation. In most cases cancer cells as well as normal cells are, as far as we can determine now, potentially immortal, which means that, given proper conditions for existence, they can live indefinitely and survive indefinitely the organism of which at one time they formed a part. Certain normal tissues may also not only live indefinitely, but also grow indefinitely, and cancerous cells differ from normal cells merely in their excessive proliferative function and in their greater power to attack the deeper tissues. This surplus power has been attained under the influence of the external stimuli which we mentioned before, with or without the cooperation of the internal factors.

The essential problem then is: How does it come about that under certain conditions stimuli which apparently are only temporary lead to changes which continue indefinitely after the stimulus has ceased to act? We must assume then that the organization of the cell has changed from one equilibrium—that of the normal cell—to another, which latter is characterized by greater proliferative activity and a greater power to penetrate into deeper tissues. The organization of some cells has been changed under the influence of growth stimuli and they are now somehow machines of a different character, which react differently to external factors. We might call such a transformation a mutation, and we have analogies for such a change in similar transformations which may suddenly occur in germ cells and lead to the production of new varieties and species. We have also in the case of ordinary tissue cells (in contradistinction to germ cells) some evidences that certain changes induced by external factors may be transmitted at least in some degree to succeeding generations of ordinary tissue cells. This is true of tissue cells as well as of germ cells; for tissue cells are potentially similarly affected as cancer cells. It is obvious then that one explanation for the origin of cancer may be the following. All or almost all normal cells possess two equilibria: (1) the equilibrium which is manifested under ordinary conditions, in which the cell has a limited proliferative power and (2) an equilibrium in which the cell has a greater proliferative power. A normal cell which has been changed from the first to the second equilibrium we call a cancer cell.

There is, however, another alternative in explaining the cancerous transformation, which would in certain respects furnish a simpler explanation. If we assume that in addition to the conditions which are important for the origin of cancer (namely, the internal and external factors before mentioned), there is hidden a constantly acting stimulus within the tumor, then the reaction of the tumor cell would be essentially similar to that of any normal cell. The tumor cell would react constantly through an increased proliferative activity merely as a result of an eternally acting stimulus. Such a continuous active stimulus working through an agent external to the cancer cell could only be supplied by a microorganism constantly at work within the tumor. By microorganism we mean a very small living organism of either plant or animal character which can be seen only microscopically and which is sometimes so small as to escape detection even under the microscope. The smallest organisms of this kind are able to pass through a filter which retains ordinary bacteria. We know, in fact, that certain microorganisms may cause tumor-like cell proliferations, especially in plants. Certain plant tumors have been shown to be definitely caused by bacteria. In the case of animal tumors the proof that microorganisms are present has so far not been definitely established. We know, however, of very interesting experiments in which tumors have been produced artificially without a transfer of the tumor cells themselves. In ordinary experiments we can readily transfer tumor cells from one individual to another, of the same species, and thus cause in the second individual the growth of the same kind of tumor. Above, in speaking of these artificially produced cancers, I had not in mind the sort that are produced by transmission of cancerous cells, but I referred especially to experiments carried out by Peyton Rous with certain *bird* cancers in which *filtrates* of the bird cancer *free from living cells* appeared to call forth the production of new similar tumors. There are other experiments on record in which the introduction of one kind of tumor stimulated the cells of the animal to the production of another kind. These results can be explained only in one of two ways: either extremely small microorganisms were transferred with the tumor filtrate, or a certain chemical substance which stimulated the tumor cells to proliferate and which was constantly produced within the tumor cells was transferred with the filtrates, or, in other cases, with the living tumor cells, into the other individual and there produced the new formation of tumors. It is very probable that it will be possible to determine experimentally which of these two alternatives is correct, and thus arrive at a definite conclusion of the problem which we are seeking to solve. This will be the last link in the chain of factors determining the origin of cancer.

It is therefore not justifiable to state, as has been constantly affirmed only a few years ago, that the cause of cancer is unknown to us. In fact, we do know perhaps the principal factors with the result that in animals at least we can decrease or increase at will the cancer rate of certain strains by regulating the factors which we have analyzed so far. The next step will be to determine whether extremely small organisms or chemical substances are present in addition to the known factors. But even if we should have answered this last question, new problems will arise as to the manner in which chemical agencies (through which probably also microorganisms would ultimately act on the cells) can cause cell proliferation. And with this problem cancer research will have reached common ground with general biology. The question of why certain stimuli cause certain cells to grow is one of the most important and far-reaching problems of general biology, since it is fundamental for both plant and animal life.

Equally important from the general biological point of view is the question of how heredity can determine whether or not certain external agencies will be more or less effective in changing the growth processes of a certain organism. But here also the problems of the origin and growth of cancer are in closest relation with other problems of biology.

To recapitulate then briefly what we know about the causes of cancer, we may make the following statment. We know the principal internal and external factors which cause cancer. We can experimentally modify or manipulate the internal and external factors in such a way as to change profoundly the cancer incidence in certain animals. By making appropriate matings between families of mice we can at will produce strains rich in cancers and strains poor in cancer. By changing internal secretions we can in certain strains of mice reduce the cancer rate from as much as 60 or 70 per cent. to nine per cent., provided the experimental interference is carried out at an early period in life. The problem which is not yet definitely solved concerns the manner in which those external and internal factors combine to cause cancer. We saw that there are two possibilities: It is possible that these factors cause a transformation of one cell equilibrium into another—the cancer equilibrium—and this would in the main differ from the cell equilibrium of ordinary life in the new production or in the greater production within the cells of the specific substance which causes abnormal growth. The same substance which would be newly produced in cells in the new equilibrium would also if injected into other animals of the same species, cause the transition of a cell from normal to cancerous equilibrium. In other words, through injection of those substances it is possible to produce a new cancer experimentally.

The second possibility is as follows: The external and internal factors which we mentioned make it possible for microorganisms to enter the tissues and to cause a transformation into cancer, or else they make it possible for a microorganism that has entered the tissues to initiate cancer growth. We are justified in believing that it will in the future be possible to decide between these two alternatives and thus to complete the solution of the problem.

Let us now turn to another phase of the cancer problem and try to answer the question, "Does the body that is invaded by cancer cells react against the cancerous growth; are in other words any mechanisms of defense apparent in the animal in which cancer is growing?" Before answering this question we must emphasize the very great distinction which exists between the spontaneous cancer, which has so far been our main consideration, and the experimental cancer. In the latter we have to deal in almost all cases with a transfer of cancerous cells from one animal to another, while in the spontaneous cancer some of the cells of the animal itself become cancerous. In experimental cancer, then, usually cells of another animal grow within the inoculated individual. This distinction is of great importance when we come to consider the defensive mechanisms that arise within the body of the animal against the inroads of the cancer cells. We may briefly point out that spontaneous defensive mechanisms arise only in the case of experimental tumors (experimental tumors are foreign cells introduced into another organism and growing there), the body does not react defensively against spontaneous tumors. It is important to note that the defensive mechanism provided by the body against the attack of cancer cells can be artificially increased. This ability to bring into action defensive mechanisms we call immunity. The immunity produced in the case of experimental tumors, is, under ordinary conditions, not an immunity directed against the causative agent of the tumor associated with the cells and being either, as we have seen, a certain chemical body or a microorganism, but against the transplanted cells. Usually no immunity can be produced in the organism in which the cells have originated. But immunity can be produced against cells that are foreign to the organism—transplanted into it. The phenomena with which we deal in the process of tumor immunity are therefore not peculiar to tumors, but are the same in every case of transplantation of tissues. No defensive mechanism is developed in the individual against the cells of his own body, only against foreign cells. Thus if we excise a bit of skin or of the thyroid gland or of the uterus and place it in a pocket under the skin, the tissue remains preserved almost intact for a long period, probably during the entire lifetime of the individual. But if, on the other hand, we transplant a piece of skin from another individual of the same species, we find that the tissue is, after a longer or shorter period, destroyed within the new host. If we make careful microscopic examinations of tissue transplanted into a new host, we find that certain cells which circulate in the blood and lymph emigrate from the vascular channels of the organism in order to invade and gradually destroy the transplanted tissue. Other cells of the host also exert a deleterious effect on the foreign tissue and contribute to its final destruction.

If, instead of transplanting tissue from one individual to another of the same species, we inoculate an individual of a different species the tissue usually perishes directly through the influence of the body fluids which are poisonous for the transplanted tissue.

How can we explain these facts? We must assume that every individual of a certain species differs in a definite chemical way from every other of that species, and that in its chemical constitution an animal of one species differs still more from an animal of another. Every cell of the body has a chemical character in common with every other cell of that body and also in common with the body fluids; and this particular chemical group differs from that of every other individual of the species and to a still greater degree from that of any individual of another group or species. Thus it happens that cells belonging to the same organism are adapted to all the other cells of that organism and also to the body fluids, but when transplanted into another organism, that specific substance which is peculiar to the individual is more or less toxic, or poisonous, for the new host, and causes the latter to react defensively against it by producing new substances which appear in the circulation and change the transplanted tissue. The transplanted tissue thus modified seems to exert an attraction for certain cells of the new host which hasten to the place in order to attack it. Or perhaps the transplanted tissue is directly altered by the foreign-body fluids and as a result defensive cells of the host are called into action.

Conditions are very similar when we deal with tumors instead of with normal tissue. Tumors which originate spontaneously in a certain individual can usually be transplanted without difficulty into another place in that individual. The cells remain alive and continue to multiply at the new place; but cells of a tumor when transplanted into another individual of the same or different species are destroyed, just as we saw was the case with the normal tissue. At this point, however, there is a difference between normal and cancerous tissue. While normal tissue in all cases is destroyed sooner or later after transplantation into another individual, there are *certain* tumors which in contradistinction to the large majority of tumors will grow in another individual of the same species after transplantation and sometimes even in an individual of a nearly related species. While structurally these *transplantable* tumors behave like other tumors, they differ from the large majority and from normal tissue in that they show a decreasing sensitiveness to the toxic action of those substances which differentiate one individual from another. These are the tumors which are used for experimental purposes. But, while it is true that these tumors will grow in a new host, it is not true that the cells of the new host are in all cases chemically like those of the tumor. Indeed, there is a difference which again makes it possible for the host to call into action certain defensive mechanisms against the invader, but these, under ordinary circumstances, are not strong or active enough to defeat it. There are, however, conditions which make the defensive action of the new host victorious over the inoculated tumor, and then it is destroyed. It is possible experimentally to increase the production of these defensive mechanisms.

There are certain tumors which grow in a new host of the same species for some time until, as a result of this growth, certain substances are produced by the host which cause the tumor first to stop growing and later to retrogress, become smaller, and finally to disappear. Other tumors may grow continuously without disappearing if transplanted into related strains of the same species. But if they are transplanted into different strains then they either can not grow at all or after temporary growth begin to get smaller and disappear. Thus it has been possible to demonstrate by experimental methods that there are fine chemical differences not only between different species and between different individuals of the same species, but also between different sets of families which constitute a strain, for certain chemical characters differentiate them from other strains of the same species. It has been shown, for instance, that white mice bred in Europe differ chemically from white mice bred in America, although the appearance of both strains may be identical. If we transplant an inoculable tumor of an American white mouse into a European strain, we find that such a tumor does not grow or that after a period of growth it becomes smaller, while in the American mice it does grow.

That certain chemical substances may become active to protect the new host against a transplanted tumor even if it does grow continuously can be shown by means of a second inoculation of the same kind of tumor and the same individual. We usually find that the growth of the first tumor has some inhibiting effect on the growth of the second tumor, but this inhibiting effect differs with different tumors. We must therefore assume that different tumors after transplantation into other animals of the same species contain a substance which characterizes the individual from which the tumor cells are derived more or less in the same way as the normal cells of an individual do, and that this differential substance calls forth protective mechanisms on the part of the host. Some tumors possess this differential substance to a lesser degree than others, or they are less sensitive to the defensive mechanism which is called forth in the host and they can therefore be more readily transplanted into other individuals.

As we stated before, it is possible to increase artificially the extent of this defensive reaction on the part of the host. We can accomplish this in a way similar to the one we used in the case of inoculation of bacteria. If we wish to produce a substance which is protective against a certain bacterium, we inject small quantities of dead bacterial substances or of the living bacteria after their virulence has been decreased, into the animal. Under the influence of these *vaccines,* as they are called, a certain immunity is frequently produced in the individual. If later we inject the fully virulent organism into the animal, it is often able to withstand the infection to which an animal not so treated would succumb. Now in the case of cancer the hostile agents against which we have to protect the animal are the cancer cells taken from another individual which grow in the new host. If, instead of inoculating bacteria we inoculate normal tissue cells from another individual of the same species or tumor cells which happen not to grow in the inoculated animal, we find that after a certain time a kind of immunity is produced in that animal. If later we inoculate that animal with fully virulent tumor cells, this tumor very frequently does not grow. As we stated before, the majority of spontaneous tumors can not very well be transplanted. It is therefore comparatively easy to find a tumor which does not grow after inoculation, but which, nevertheless, forms a protective substance fatal to the growth of a virulent tumor. Now, while it is frequently possible to immunize against bacteria with dead bacteria or with certain extracts of bacteria, this is not possible in cancer immunization. Here we have to inoculate with living cells which only gradually die if transferred into the new host. Apparently a certain product of metabolism of the introduced cells, perhaps some product of oxidation, is necessary for this purpose, and such an oxidative process seems to take place only in the living cell.

How can we then interpret the mechanism which leads to the setting at work of these protective agencies? The most probable explanation is as follows: If the cell from the same species, but containing a differential chemical substance, is introduced into another individual, it attracts either directly certain wandering cells of the blood, which invade the tumor and also cause the connective tissue cells to form denser fibrous bands around the tumor, thus cutting off the nourishment from the transplanted cells, or such an effect is produced in an indirect manner. The differential chemical substance in the cells calls forth the new production of a chemical immunizing substance which circulates in the blood, or calls into action a substance which was already preformed in an animal and which it was not necessary to produce artificially. But even in the latter case an additional new formation of such an immunizing substance is added to the first substance which was preformed; these substances act upon the introduced cells, change their metabolism in a more or less injurious manner and call forth the reaction on the part of the wandering cells of the blood and of the connective tissue cells. We find, therefore, that in the case of tumors the reaction is exactly the same as with the transplanted normal tissue.

As stated before, after the so-called homoiotransplantation of tissue —a transplantation into another individual of the same species—certain wandering cells of the blood as well as the connective tissue are the principal agents in destroying the invading tissue. But just as in the case of auto-transplantation of normal tissue—a transplantation into the same individual in which it originated—no antagonistic reaction is called forth on the part of the wandering cells and connective tissue, and no defensive reaction takes place, no chemically immunizing substance is formed against a spontaneous, autochthonous tumor. We find, therefore, that, after transplantation into another individual, cancers not rarely retrogress spontaneously. But such retrogression hardly ever occurs in a spontaneous tumor within the individual that produced it. And, moreover, not only does such a spontaneous retrogression not usually occur in spontaneous cancers, but we usually are not even able to produce experimentally a defensive mechanism such as appears when a transplantation occurs into another animal of the same species. Vaccination with either normal tissue or with tumor tissue that does not grow is of little or no avail for restricting the growth of spontaneous tumors.

We have now discussed the origin of tumors and the protective reaction in the body against tumor growth. There remains the third field upon which cancer research has shed new light. I refer to the character, conditions of growth and life of tumor cells in particular and of normal body cells in general. As has already been stated, the continuous transplantation of tumors has made very evident one fact of great biological significance, namely, the potential immortality of ordinary body cells. It had been assumed formerly that unicellular organisms like protozoa and bacteria as well as the *germ* cells—especially the ova of metazoa including the vertebrates—are potentially immortal. Provided no accident takes place, one protozoon can give origin to an endless chain of new individuals of the same species. In a similar way the germ cells of a multicellular organism, for instance, of a vertebrate, develop after fertilization into adult organisms; certain cells, however, fail to undergo the differentiation which other cells do and they form later on the germ cell—the ovum or sperm cells—in the new individual. Through fertilization they again are preserved and again give rise to a new generation of germ cells. In this way germ cells are potentially immortal, while all the other cells of the body, which, in contradistinction to germ cells, are called somatic cells, die with the individual. Now it was supposed that the death of the somatic cells was not an accident, but a necessary event distinguishing somatic cells from germ cells. This view cancer research has shown to be incorrect. We now know that most of the cells of the body are potentially tumor cells and we also know that tumor cells are potentially immortal, in the same sense as protozoa and germ cells. When we speak of "*immortality*" we must of course take into consideration the fact that periods of time which man can observe are always finite quantities and that to use the term immortality is to deal with only approximations. If then somatic cells usually die, it is due to a more or less unfavorable environment, conditions which we can not control at the present time.

There are some other interesting conclusions regarding cell life, to which cancer research has led. We have shown that it is possible to increase and to decrease the growth energy of tumor cells at will by artificial means. If we expose tumor cells in test tubes to certain degrees of heat or cold before inoculating them into the new host, or if they are subjected to the action of certain injurious chemicals which are not sufficiently strong to kill the tumor cells, we find that the subsequent tumor growth following inoculation is very much impaired and weakened. These procedures, therefore, interfere with the action of those mechanisms which are responsible for cell multiplication. On the other hand, it is almost invariably possible to increase the virulence of tumor cells by subjecting them to mechanical stimuli, such as cutting into the tumor. Thus it comes about that tumors which recur after incomplete extirpation usually grow more rapidly than the original tumor. These observations make it very probable that the growth energy of somatic cells in general can be increased and decreased in a similar way and that the increase in growth energy in cancer cells is similar to that observed in normal cells in case of wound healing. In both cases mechanical stimuli increase growth energy.

There is a third class of observations of great biological interest that concerns the transmission of changes produced in one cell generation to another which itself has not been exposed to these changes. Thus it has been found that it is possible through the action of certain chemical substances which, for instance, may be injected into a vein and which reach the tumor only through the circulation, to produce a remarkably inhibiting effect on the growth of the transplanted tumor and in some cases even to cause its retrogression and disappearance. But we also found that through such injections the tumor cells become immunized against the action of these substances, that the effect, therefore at present is only a temporary one, and that this immunity is transferred to the next cell generation which had not been exposed to the action of the chemical. Thus in the case of somatic cells, as in the case of protozoa and bacteria, changes produced by external agencies may be transferred to at least a certain number of the following cell generations. And the same seems to take place in the case of germ cells—as in the effect of alcohol for instance—an effect transmitted to cell generations not directly exposed to the action of the poison.

If we survey what we have said of the methods and results of cancer research, one conclusion especially impresses itself upon us, namely, that there is a very close connection between cancer research and general biology. In cancer research, whether we deal with the origin of cancer, the reaction of the body against it, or the conditions favorable to its growth, we have to do in each case with the properties of cells, and these properties as seen in the cancer cell can not be understood without a constant reference to the normal cells from which it was derived. And conversely, our knowledge of the life of the normal cell, which is essentially the problem of general biology, is broadened and deepened through cancer research. Cancer research is, in fact, a department of comparative general biology, and its fate is closely bound up with that of other biological sciences.

In closing I shall say a few words in regard to the practical application of cancer research—the prevention and treatment of the disease. We have found that there are internal and external factors concerned in the origin of cancer. Of the internal factors, heredity and the presence of certain malformations play a very prominent part in the development of cancer, unquestionably in animals and probably also in man. Of the external factors long-continued stimulation, long-continued irritation, of tissues is one of the important causative conditions. If we wish to prevent cancer we must be able to control all these factors. It is comparatively easy to do this in the case of external factors. Long-continued irritation of any sort must be avoided. Under certain conditions, for instance, it might be wise to remove all pigmented moles which are exposed to irritation. The control of the factor of heredity is more difficult. It would be one of the problems of eugenics. The difficulty, however, in applying theoretical knowledge in this field is two-fold: in the first place, living organisms are a great complex of hereditary unit factors, which are transferred from generation to generation independently of one another. This makes a selective mating very difficult. Advantageous factors are combined in the same organism with inferior ones, and it is at present almost impossible—at least in most cases—to determine which factors merit greater consideration, especially when we consider that the large majority of hereditary unit factors in the case of the higher organisms are almost unknown to us. The second difficulty in practical eugenics is the danger that methods which might be suggested for certain purposes would be contrary to that social understanding and sympathy which is the basal factor of our civilization. All we can say at present is that it might be advisable to avoid interbreeding between strains in both of which the tendency to cancer is dominant. But in the case of man even this conclusion can, at the present time, be drawn in only a tentative way.

As to the treatment: Science shows us that cancer starts as a local disturbance, and, from what we have learned, it follows that the earlier the local growth is completely eradicated the better will be the results. For this eradication surgical means should be employed in the large majority of cases. In a few selected cases some other methods might be indicated. Certain methods, depending on the application of different principles, are at present still of an entirely experimental character. How far it will be possible to develop them in the future we are not able to foretell. The investigator must follow his path quietly, guided by purely scientific aims. This will be the surest method of bringing about the greatest practical results.